Self-Reported Cognitive Impairment in Patients With Cancer

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Abstract

Purpose: Cancer patients often report cognitive impairment, manifested as problems with concentration and memory, following cancer therapy. As part of a large multicenter survey of cancer patients undergoing treatment, we investigated the frequency and severity of self-reported problems with memory and concentration over time.

Methods: A total of 595 patients undergoing treatment for solid tumors self-rated problems with memory and concentration, using an 11-point Likert scale (0 = "not present" to 10 = "as bad as you can imagine") at baseline before treatment began (T1), at their worst during treatment (T2), and at 6 months following treatment (T3). Any symptom level ≥ 7 was classified as "severe." Paired or independent *t* tests (as appropriate) with a Bonferroni correction were used to examine differences in symptoms over time and between patients treated with chemotherapy, radiation therapy, or both.

Results: Concentration problems were reported by 48% of the 595 participants at T1 (5% severe), 67% at T2 (18% severe), and 58% (8% severe) at T3. Problems with memory were reported by 53% at T1 (4% severe), 67% (18% severe) at T2, and 68% (11% severe) at T3. The average frequency and severity of both symptoms in patients receiving chemotherapy, with or without radiation, increased significantly between T1 and T2 ($P < .001$). Both symptoms were less severe in patients receiving radiation alone at all three measurements than in either of the chemotherapy groups (all P values $< .001$). Symptoms at T3 were significantly higher than T1 for all groups ($P < .001$).

Conclusion: A significant proportion of patients undergoing cancer therapy self-report problems with memory and concentration. Cognitive problems get worse during treatment and are still in evidence 6 months following the conclusion of treatments.

Introduction

Nausea, anemia, and fatigue are all well-known adverse effects of chemotherapy. Along with such physical ailments, accumulating evidence suggests that chemotherapy and radiation therapy affects cognitive functioning in some patients as well.[1–4] The cognitive frustrations (dubbed "chemobrain" by cancer survivors) refer to a range of difficulties that tend to include relatively subtle changes in memory, concentration, and executive function that can emerge in the weeks during cancer treatment and months after its completion. These difficulties have been reported in a variety of solid tumor cancer diagnoses, including breast cancer and other malignancies in which chemotherapy does not target the brain itself and can have a significant adverse impact on the quality of life.[2,5–10] Although research continues, there is a paucity of longitudinal information about the frequency and severity of self-assessed cognitive impairment. The objective of the present article is to add to this literature by reporting on the occurrence and severity of two commonly reported cognitive symptoms in a nationwide sample of patients who were surveyed with a self-administered questionnaire prior to, during, and 6 months after completion of cancer treatment.

Methods

Data were collected as part of a longitudinal study funded by the National Cancer Institute, designed to assess the information needs of newly diagnosed cancer patients scheduled to undergo chemotherapy or radiation therapy or a combination of both. Study participants (N = 1,015) were outpatients at 17 private oncology practices enrolled between January 30, 2001, and September 13, 2002, that were members of Community Clinical Oncology Program (CCOP) and affiliated with the University of Rochester Cancer Center (URCC) CCOP Research Base. Prior surgery was allowed, but not prior chemotherapy or radiation therapy. Patients with diagnoses of breast, lung, prostate, hematologic, gastrointestinal, or head and neck malignancies were accrued to the study before their first treatment. The University of Rochester Research Subjects Review Board and internal review boards for each participating CCOP site approved the study, and written informed consent was obtained from each participant before data collection.

Measures

Demographic data and participant self-rating of general health status (excellent, very good, good, fair, or poor) were obtained through a brief clinical interview and self-report questionnaires that were administered at three time points: (1) within 2 weeks before the initiation of chemotherapy and/or radiation therapy (baseline), (2) within 2 weeks of completing treatment (post-treatment), and (3) 6 months after completion of treatment (follow-up).

The enrolling physician was asked to assign a Karnofsky performance status for each participant at each time point. Current symptoms were assessed using a symptom inventory that was adapted from a measure developed at The University of Texas M.D. Anderson Cancer Center.[11] The Symptom Inventory is a

series of uniscales in which the severity of each symptom is indicated by filling in the appropriate circle on an 11-point Likert scale anchored from 0 ("not present") to 10 ("as bad as you can imagine"). A score of greater than 7 was categorized as "severe." Questions asked were "Your problem **remembering things** at its **WORST?"** and "Your difficulty **concentrating** at its **WORST**?" Participants were instructed to respond to the adverse effect questionnaire administered after completing treatment with answers that reflected their adverse effect severity at its worst at any point during treatment. Responses to the questionnaire administered pretreatment and 6 months posttreatment were based on symptoms experienced during the previous 5 days.

Statistical Analysis

Data analysis was performed using SPSS software (version 12.0; SPSS Inc, Chicago, Illinois). Independent or paired *t* tests and paired or independent χ^2 tests were used as appropriate with a Bonferroni correction to examine differences in symptoms over time and between patients treated with either chemotherapy, radiation therapy, or a combination of both. Multivariate analysis of variance was conducted to detect differences between groups.

Results

Subject Characteristics

Of the 1,015 patients enrolled on the study, 595 (59%) provided assessable data at all three time points. Only data from these 595 participants are included in these analyses. The majority were white (n = 561, 94%), 437 (73%) were married, and 343 (57%) had at least some college education. The most common cancer diagnosis was breast cancer (n = 320, 54%), followed by genitourinary cancers (n = 118, 20%). There were 220 respondents who were treated with chemotherapy (37%), 239 who received radiation therapy (40%), and 136 who received both types of treatments (23%). Self-rated health was "excellent" or "very good" in 67% of the sample (n = 399). Four hundred and twenty participants (41%) were excluded from the analyses because they did not provide assessable data at all three time points. The characteristics of the participants who were excluded were similar to those who were included being mostly white (n = 367, 90%), female (n = 249, 61%), and college educated (n = 210, 50%), with a predominance of breast cancer diagnoses (n = 149, 37%). Treatments received were also similar to the group included in the final analysis: 176 (43%) received chemotherapy, 96 (24%) received radiation therapy, and 111 (27%) received both. The remaining 37 received no chemotherapy or/and radiation therapy. The demographics and clinical characteristics of the study population are presented in Table 1.

Analyses

Memory loss and problems concentrating were reported by nearly half the study population at baseline, and increased substantially during treatment in all three groups. These problems were significantly greater in women (n = 395, 66%) than men (n = 200, 34%) during (both symptoms, $P < .001$) and posttreatment (both symptoms, $P < .001$) but not at baseline (both symptoms, $P > .05$). Neither of the two symptoms had returned to baseline within 6 months following the end of cancer treatments, and each continued to be experienced by a majority of patients. As presented in Table 2, memory loss was reported by 53% at baseline (30% mild, 19% moderate, 4% severe), 67% during treatment (24% mild, 25%, moderate, 18% severe), and 68% at follow-up (27% mild, 30% moderate, 11% severe). These reports at baseline are of all those patients who gave a nonzero answer to the questions asked. Problems with concentration were reported by 48% of participants at baseline (26% mild, 18% moderate, 4% severe), 67% during treatment (26% mild, 24% moderate, 17% severe), and 58% at follow-up (26% mild, 24% moderate, 8% severe). A 3 × 3 (condition-time-outcome) repeated-measures multivariate analysis of variance, with severity of memory loss and concentration problems as the dependent variables, showed a statistically significant interaction ($P < .001$). An examination of the main effects showed a statistically significant difference for condition ($P < .001$) and for time ($P < .001$). Pairwise comparisons as part of the main analysis indicated significant differences for the average severity of both memory and concentration problems between the radiation-alone group and the chemotherapy-alone group, and also between the radiation-alone group and the radiation/chemotherapy group (all $P < .001$), but no statistically significant differences between the chemotherapy-alone and the radiation/chemotherapy groups ($P > .05$). Of the 420 participants who provided only baseline data, 50% reported memory loss, and 47% reported problems concentration. These data are comparable to the responses given by the sample at baseline that went on to complete assessment at all three time-points.

We conducted further analyses of variance to examine memory and concentration change scores over time (ie, during treatment minus baseline reported problems) among the three treatment groups. Overall, both symptoms were statistically significant between groups at baseline and during treatment, and baseline and follow-up (all *P* values $< .001$). However, no statistical significance was found between groups in problems concentrating between baseline and follow-up ($P > .05$). Memory and concentration problems were also less severe in patients receiving radiation alone during and posttreatment (all *P* values $> .05$) than in either of the chemotherapy groups, as shown in Figures 1 and 2. Comparisons of symptom severity across treatment groups are summarized in Table 2.

Discussion

The results of this longitudinal multicenter study of 595 cancer patients receiving chemotherapy, radiation therapy, or both, provide further evidence that cognitive impairment is a debilitating and prevalent adverse effect, and parallel the growing literature suggesting that cognitive problems are associated with

Table 1. Demographic and Clinical Characteristics at Baseline (N = 595)

	Chemotherapy Alone (n = 220)		Radiation Alone (n = 239)		Both (n = 136)	
	No.	%	No.	%	No.	%
Age, years						
Mean	57.8*		66.07*†		56.3†	
Standard deviation	12.2		10.8		12.9	
Range	21-82		31-88		29-92	
Sex						
Male	54*	25	121*†	51	25†	18
Female	166	75	118	49	111	82
Race/ethnicity						
White	210	96	224	94	127	93
Black	7	3	13	5	6	4
Other	1	1	2	1	3	3
Education						
Some college	124	56	141	59	78	57
High school or less	96	44	98	41	58	43
Marital status						
Married (n = 437)	165	75	174	73	98	72
Not married (n = 158)	55	25	65	27	38	28
Previous surgery	177*	81	164*	69	106	78
Primary cancer site						
Alimentary tract	31	14	1	0	7	5
Breast	125	57	98	41	97	71
Genitourinary tract	7	3	107	45	4	3
Gynecologic	13	6	12	5	6	4
Hematologic	29	13	7	3	5	4
Lung	13	6	10	4	16	12
Other	1	1	4	2	1	1
Karnofsky performance status						
Mean	92.6*		95.4*		95.0*	
Standard deviation	11.0		8.9		7.4	
Range	60-100		60-100		60-100	
Self-rated health status						
Excellent	47	21	80	33	50	37
Very good	100	46	79	33	43	31
Good	58	26	61	26	34	25
Fair	13	6	17	7	9	7
Poor	2	1	2	1	0	0

* and † There was a significant difference between these groups ($P < .05$).

cancer and its treatment. We observed that a significant proportion of patients undergoing cancer therapies self-report problems with memory and concentration in all three treatment groups at all three assessment points. In summary, the frequency and severity of self-reported problems with memory and concentration peaked during therapy and although symptoms at six month follow-up were significantly higher than pretreatment for all groups, average levels of severity at six

Table 2. Comparison of Symptom Severity Across Treatment Groups (radiation, chemotherapy, or both) and Periods (pretreatment, during treatment, and post-treatment)

	Patients Reporting Difficulty (%)		Mean Severity (with difficulty)	SE_{wd}	Mean Severity (all patients)	SE_{ap}
	No.	%				
Memory						
Radiation alone						
Baseline	125	52.3	2.61	0.17	1.36[a]	0.12
During	116	48.5	3.66	0.24	1.78[1,3]	0.17
Follow-up	141	59.0	3.36	0.19	1.98[a,2,4]	0.16
Chemotherapy alone						
Baseline	120	54.5	2.72	0.18	1.48[b]	0.14
During	180	81.8	4.39	0.20	3.59[b,1]	0.20
Follow-up	168	76.4	3.83	0.19	2.93[b,2]	0.18
Both treatments						
Baseline	69	50.7	2.90	0.25	1.47[c]	0.18
During	103	75.7	4.71	0.28	3.57[c,3]	0.27
Follow-up	96	70.6	3.89	0.24	2.74[c,4]	0.23
Concentration						
Radiation alone						
Baseline	94	39.3	2.84	0.23	1.12[w,x]	0.13
During	102	42.7	3.77	0.28	1.61[x,5,7]	0.17
Follow-up	105	43.9	3.37	0.23	1.47[w,6,9]	0.15
Chemotherapy alone						
Baseline	123	55.9	2.57	0.17	1.44[y]	0.13
During	189	85.9	4.55	0.19	3.91[y,7]	0.20
Follow-up	151	68.6	3.34	0.18	2.30[y,6]	0.16
Both treatments						
Baseline	70	51.5	2.96	0.27	1.52[z]	0.19
During	108	79.4	5.11	0.26	4.06[z,5]	0.27
Follow-up	94	68.9	3.60	0.25	2.41[z,9]	0.22

NOTE. Only patients who reported > for symptom severity; wd = with difficulty, ap = all patients. Identical superscript letters indicate a statistically significant difference **within** groups ($P \leq .05$). Identical superscript numbers indicate a statistically significant difference **between** groups ($P \leq .05$).

months post-treatment remained significantly worse than that before treatment.

A majority of the participants reported problems with impairment before beginning therapy. Our findings coincide with what has been reported previously. For example, one of the few research groups who have collected data on patients before treatment found that a substantial proportion of patients had impaired cognitive function before the institution of chemotherapy.[12,13] Several factors, such as receiving general anesthesia during surgical procedures or the stress associated with the diagnosis and staging of cancer, may contribute to abnormal pre-chemotherapy assessments. Although the general pattern of symptom severity getting worse during treatment and then recovering following treatment conclusion, but not going back to baseline levels, is similar between therapy groups. Memory problems in the radiation group during treatment do not follow this pattern.

Limitations

There are several limitations of this study. The patients in this study tended to be more educated than the general population and were primarily Caucasian, making this study less generalizable to patients from minority groups or to people with lower socioeconomic status. Also, cancer patients in this study sample were treated as outpatients in community cancer treatment cen-

Figure 1. Difficulties with concentration over time, by treatment type.

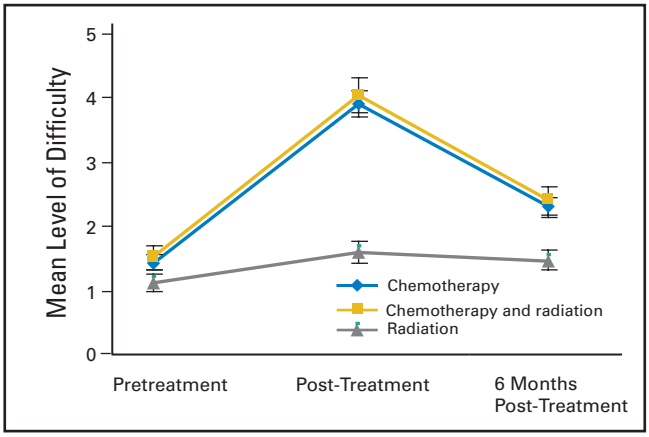
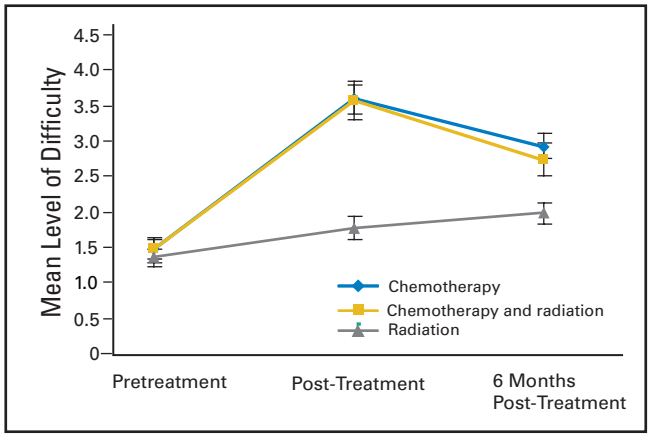


Figure 2. Difficulties with memory over time, by treatment type.



ters and the findings may not be representative of all cancer patients, especially those with more severe or rare cancers that required inpatient hospital care. In addition, we did not have information on whether or not study participants were on antiestrogen or antiandrogen therapy; such information would have been helpful in assessing the factors associated with self-reported cognitive complaints. The main strengths of our study are the large sample size, the variety of tumor types, and the assessment of the patients at three time points-before, during and after treatment.

Conclusion

As the indications for chemotherapy and radiation therapy expand in the face of some time diminishing marginal benefit, it is critical to understand and quantify the impact of various treatments on quality of life. Recognizing and acknowledging the side effects of treatment, and their frequency and severity, is absolutely critical and will help patients make decisions about therapy when the marginal benefit may be low. It is interesting that many patients in this study had memory and concentration problems before beginning treatment, indicating the profound effects that a cancer diagnosis has on multiple aspects of quality of life. Patients need to be counseled and educated in order to help anticipate cognitive decline. Detecting cancer treatment–induced cognitive decline, particularly in its earlier stages, is increasingly important because recognition of cognitive impairments permits provision of early counseling to patients and their families, enhanced communication about symptoms, treatment decisions, and identification of surrogate markers. In the absence of recognition of cognitive impairment, physicians have little reason to question the accuracy of patient histories and are less likely to seek corroborating information from family members.

Subtle cognitive changes pose unique challenges to detection and management. First, the cause of subtle changes in cognitive function may not be readily apparent, and the impairments may not be assessable with standard, objective neuropsychological measures. Second, subtle changes in cognitive function may also be confused with or confounded by other problems commonly associated with cancer and its treatment, such as depression, anxiety, and fatigue. Measuring self-report objectively is important, and as a recent article suggests, self-report is necessary to define the impact of the subtle cognitive deficits caused by systemic chemotherapy on daily functioning and quality of life (eg, how the cognitive deficits impact career and educational decisions, activities of daily living, and general quality of life).[14] Expanding the scope of research tools is particularly important because quality-of-life measures often used in clinical and research practice may not be sensitive enough to detect the negative impact of the cognitive problems experienced by cancer survivors. This study included patients with a variety of tumor types, treatments, varying ages, and both sexes. Additional research to identify factors that may play a role in patients' susceptibility to cognitive damage is needed. Potentially, this could lead to a prevention/treatment strategy against cognitive decline by using pharmacologic and/or behavioral interventions in the "at-risk" population of survivors. Since the number of cancer survivors has increased in the last decade, the impact on health planning in cancer survivors who are aging is both pertinent and critical at the individual and health policy level.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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